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Design, synthesis and applications of new families of chiral sulfonic acids

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ABSTRACT

Two new families of chiral arenesulfonic acids were synthesised in a short, robust and scalable synthetic sequence involving a key cross-coupling step of an aromatic scaffold with a suitable chiral auxiliary. The flexibility of the synthetic route and the ready availability of a range of naturally occurring chiral auxiliaries allowed us to prepare nine enantiomerically pure sulfonic acids with a tunable stereochemical environment. Application of the strong chiral Brønsted acids was demonstrated in an enantioselective nitrone/enol ether 1,3-dipolar cycloaddition.

1. Introduction

Stronger chiral Brønsted acids have recently emerged as powerful synthetic tools for important and often novel enantioselective bond forming reactions.[1] Arguably, the most important class is the BINOL-derived chiral phosphoric acids **1a**,**b** (BPA, Fig. 1) and related compounds introduced by Akiyama and Terada.[2] With the expansion of the field came the need for enhanced acidity, which has been realised in the form of phosphorodiamidic acid derivative **1c**[3] and *N*-triflyl phosphoramides **1d**[4] and related derivatives.[5] These derivatives can impart high levels of enantiocontrol in reactions where the original class of BPAs are either poor controllers of asymmetry or are catalytically inferior or showed no catalytic activity.[4,5] Therefore, the importance of the contribution of stronger Brønsted acids to the field is apparent, however there is an upper limit to the acidity of such classes of acids.

Accordingly, future opportunities will arise from other classes of higher acidity chiral organic acids, such as chiral sulfonic acids, which could potentially give rise to a broader range of catalytic applicability. Several enantiomerically pure chiral aliphatic sulfonic acids, including long-known camphor sulfonic acid **1i** (CSA), have been prepared for use mostly as resolving reagents.[6] The most recent examples of this class of stronger Brønsted acids are represented by enantiomerically pure sulfonic acids **1j**, which emerged from a stereoselective addition of sodium bisulfite to a suitable Michael acceptor.[7] An even higher Brønsted acidity of chiral sulfonic acid was calculated for the simplest member of BINOL-derived bis-sulfonic acids **1e** (BINSA, pK_a in DMSO −9.06).[5c] Although BINSA has been known since 1928, its applications in acid-catalysed transformations remained unexplored until 2008 when it was obtained in enantiomerically pure form.[8] Shortly after, more advanced descendants of BINSA's **1f**[8] (R = Ar, Me_3Si) and related disulfonimides **1g**,**h**[8] were synthesised.[8,9]

Recently, Enders and Blanchet reported the syntheses of novel planar chiral sulfonic acids **1k**, **1l** and novel axially chiral sulfonic acids **1m**, respectively.[10,11] We believed that enhanced reactivity and enantiocontrol, potentially in a wide range of acid catalysed reactions, could be harnessed from alternative, novel and readily accessible classes of chiral sulfonic acids. Herein we report new, efficient and general routes to a range of novel single enantiomer arenesulfonic acids and report preliminary enantioselectivity data in an acid catalysed nitrone/enol ether 1,3-dipolar cycloaddition reaction.

2. Results and discussion

Our initial design plan was to construct an arenesulfonic acid bearing two chiral appendages attached to the 2- and 6-positions, thus creating a chiral environment around the sulfonic acid group (Scheme 1). Our synthesis plan was therefore to develop straightforward, yet synthetically powerful routes through standard cross-coupling protocols (such as Ulmann, Goldberg, Suzuki, etc.) on commercial (or readily accessible) arene derivatives to afford novel stronger Brønsted-acids that could have general applicability in enantioselective acid catalysed reactions.

We designed two distinctive synthetic routes. In our first approach (Scheme 1, Route A), the plan was to first construct a chiral substituted benzene scaffold **4**, and subsequently introduce the sulfonic acid moiety. This approach would be short in step

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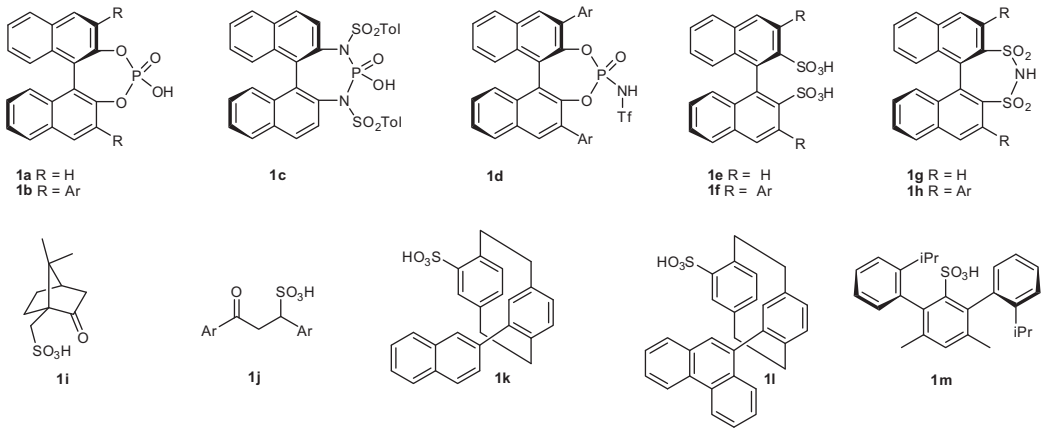
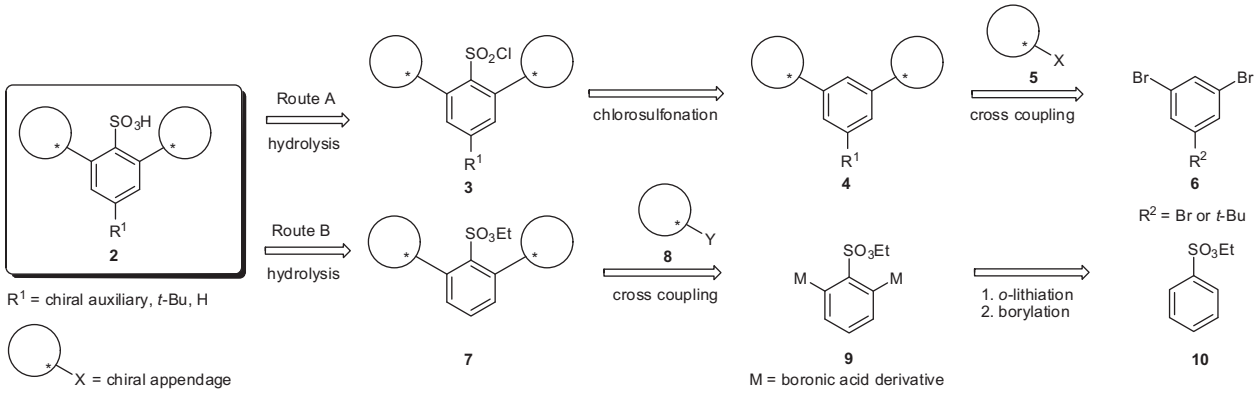


Figure 1. Selected existing stronger Brønsted acids.



Scheme 1. Retrosynthesis of novel chiral arenesulfonic acids.

count, would not suffer from regioselectivity problems and would be amenable to library generation. In our second, (Scheme 1, Route B) we planned to use a sulfonate ester **10** on an appropriate arene ring as both a directing group for the regioselective introduction of chiral appendages and a masked acid. Specifically a Snieckus directed *ortho* metalation[12] would allow the regiocontrolled synthesis of an aryl boronic acid **9** which under appropriate conditions would undergo cross-coupling with a range of chiral coupling partners. Finally a mild hydrolysis of sulfonates **7** would finish the synthesis of **2** in five steps.

2.1. Route A

In choosing the cross-coupling reaction for the synthesis of the chiral arene scaffolds, we considered the availability/accessibility of a small library of chiral appendages/auxiliaries, suitably substituted arenes, and the robustness/reliability of the coupling reaction itself. Accordingly, the well-precedented Cu-catalysed Ulmann–Goldberg coupling of suitable aryl halides with chiral oxazolidinones became our first choice.[13] Chiral enantiopure oxazolidinones **5a–d** were the nitrogen-containing heterocycles of choice since they are commercially available or easily made in both enantiomeric forms from natural or unnatural aminoacids.[14]

Using catalytic amounts of copper iodide in the presence of DMEDA and potassium carbonate, C_3 and C_2 symmetrical derivatised arenes were readily synthesised in a single operation in good yields from brominated arenes **6a** and **6b** using oxazolidinones **5a–d** (Scheme 2).

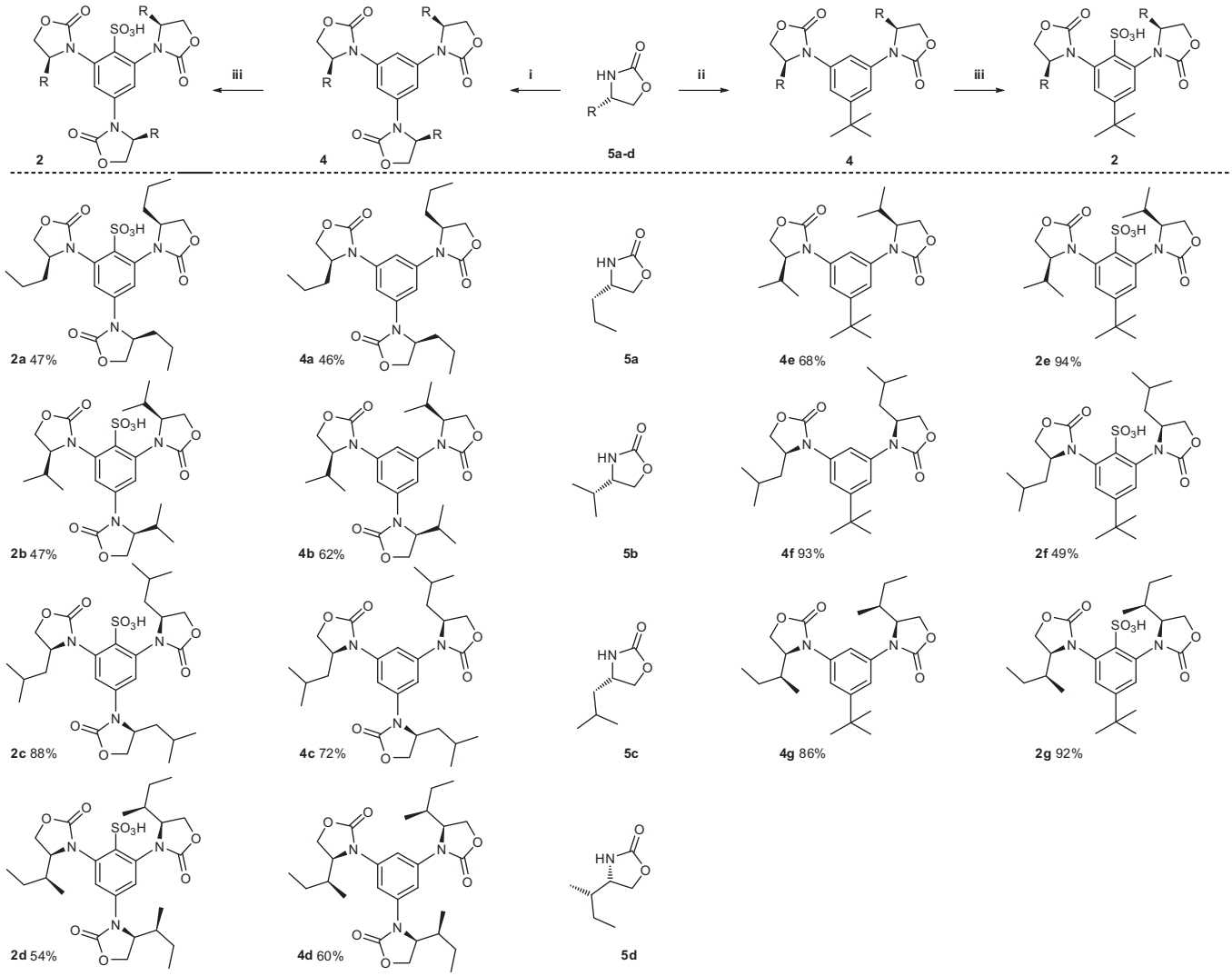
With electron rich C_3-symmetrical chiral scaffolds **4a–d** and C_2-symmetrical **4e–g** in our hands we then investigated the introduction of the sulfonic acid moiety. Using a modified literature procedure for the chlorosulfonation of 1,3,5-trisubstituted benzenes, we isolated directly the desired sulfonic acid and not the intermediate sulfonyl chloride (Scheme 2).[15] Our short route allowed us to produce significant quantities of novel chiral benzenesulfonic acids in a 2 step sequence. The structure of **2b**, was determined from single crystal X-ray diffraction studies and is reported as the hydroxonium salt in the solid state (Fig. 2).

2.2. Route B

In our first route (Route A, above) the sulfonic acid functionality was introduced in the last step of the synthesis. However, with the knowledge that arene sulfonate esters are powerful *ortho*-directing groups in the Snieckus reaction, in our second route, we decided to employ these as starting materials.[12] Treatment of ethylsulfonate **10** with butyllithium for 6 h at −78 °C,[16] followed by quenching of the lithiated intermediate with trimethylborate yielded boronic acid **11** in excellent yield via this scalable one-pot procedure (Scheme 3).[17]

Subsequent Suzuki coupling[18] with readily prepared menthenyltriflate **8a**[19] provided sulfonate **12** in good yield (Scheme 3). A second tandem *ortho*-lithiation/boronate ester quench provided boronic acid **13**, which was a suitable precursor for further diversification. Coupling of **13** with readily available triflates **8a**, **8b**[19,20] provided structurally varied sulfonates **7a** and **7b** in good yields (Scheme 4). A convenient, high yielding alkaline hydrolysis of sulfonic esters **7a**, **7b** followed by acidification with dilute HCl afforded chiral sulfonic acids **2h**, **2i**.

With a library of two classes of structurally diverse sulfonic acids **2a–g** and **2h**, **2i** in hand, our next aim was to provide a proof of principle that they were indeed capable of imparting asymmetry



Scheme 2. Synthesis of chiral arenesulfonic acids. Reagents and conditions: (i) 1,3,5-tribromobenzene, **6a**, CuI, K_2CO_3, *N,N′*-dimethylethylenediamine (DMEDA), toluene, reflux 20–30 h; (ii) 1,3-dibromo-5-*tert*-butylbenzene **6b**, CuI, K_2CO_3, DMEDA, toluene, reflux 24 h; (iii) $ClSO_3H$, chloroform, reflux, 24–48 h.

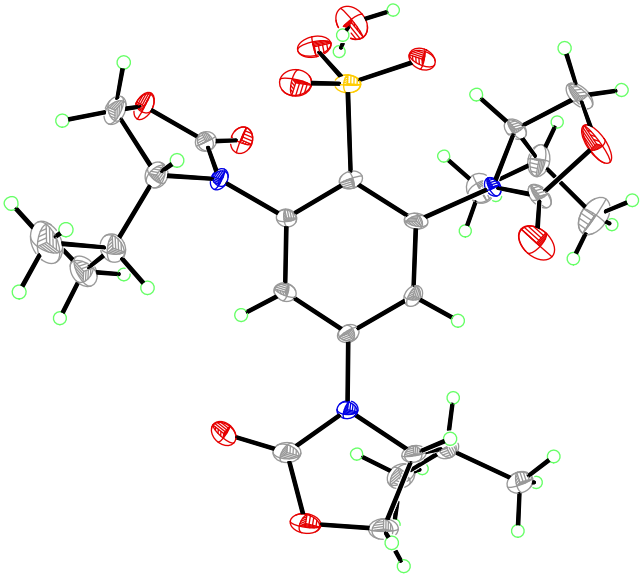
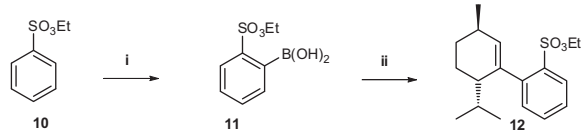
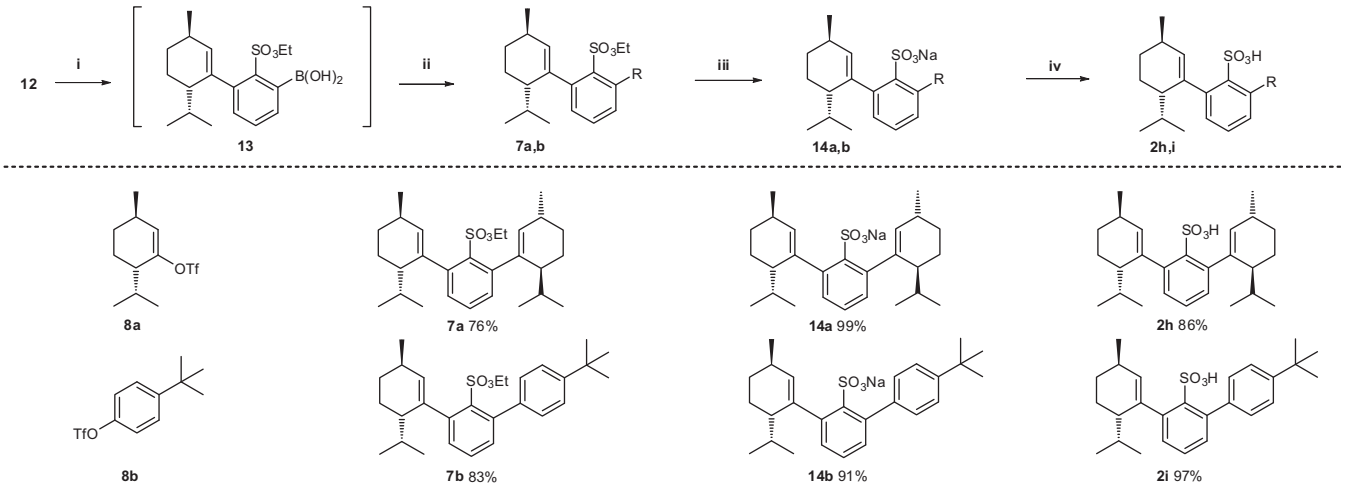


Figure 2. Thermal ellipsoids for **2b** drawn at 30% probability and selected solvent omitted for clarity. See Section 4 for details.

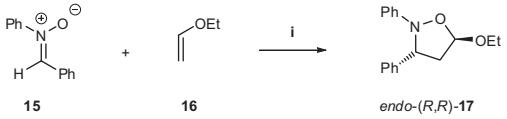


Scheme 3. Synthesis of common precursor for the divergent synthesis of chiral arenesulfonic acids. Reagents and conditions: (i) (a) *n*-BuLi, THF, −78 °C, 5 h then (b) $B(OMe)_3$, −78 °C → rt, 12 h, 92%; (ii) **8a**, Cs_2CO_3, $Pd(PPh_3)_4$, DME, H_2O, 70 °C, 1 h, 78%.

in an acid-catalysed reaction. Inspired by the recent report of Yamamoto[21] we decided to test the new chiral sulfonic acids in the 1,3-dipolar cycloaddition of nitrone **15** and ethyl vinyl ether **16** (Schemes 5 and 6). Initially, systematic solvent, temperature and concentration variations were undertaken to determine the reaction conditions for the optimal catalytic performance of acid **2b** in the 1,3-dipolar cycloaddition. This survey revealed that the best results in terms of enantioselectivity and isolated yield were obtained when the reaction was performed in chloroform at −35 °C at a moderate dilution (Scheme 5, entry 4). With the established conditions in hand, sulfonic acids **2a–g** were screened (Scheme 5, entries 3–9). In all cases a high diastereoselectivity



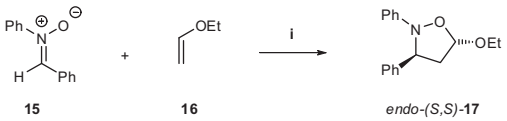
Scheme 4. Synthesis of chiral arenesulfonic acids **2h**, **2i**. Reagents and conditions: (i) (a) *n*-BuLi, THF, −78 °C, 6.5 h then (b) $B(OMe)_3$, −78 °C → rt, 1 h, ~100% (crude); (ii) ROTf **8**, Cs_2CO_3, $Pd(PPh_3)_4$, DME, H_2O, 70 °C, 2 h; (iii) NaOH, EtOH, 14 h, reflux; (iv) HCl, rt, 5 min.



Scheme 5. Application of catalysts **2a**–**g** in the enantioselective nitrone/enol ether 1,3-dipolar cycloaddition. Reagents and conditions: (i) arenesulfonic acid catalyst, 4 Å MS, $CHCl_3$, −35 °C, 24 h, for the yields and stereoselectivities, see the table below.

Entry[a]	Catalyst	*endo*:*exo*[c]	Yield[d] (%)	ee[e] (%)
1	—	—	0	—
2	PTSA[b]	80:20	78	—
3	**2a**	95:5	83	32
4	**2b**	93:7	83	30
5	**2c**	95:5	79	17
6	**2d**	93:7	83	26
7	**2e**	94:6	81	19
8	**2f**	94:6	83	8
9	**2g**	94:6	81	14

[a]Unless otherwise stated all reactions were performed on a 0.3 mmol scale, 0.05 M at −35 °C using 10 mol % of catalyst.
[b]Reaction performed at rt for 20 min under the standard reaction conditions.
[c]Determined by ^{1}H NMR of the isolated product.
[d]Isolated yield after column chromatography purification.[e]Determined by HPLC of the isolated product, ee and the absolute configuration of the minor diastereomer was not determined.



Scheme 6. Application of catalysts **2h**, **2i** in the enantioselective 1,3-dipolar cycloaddition. Reagents and conditions: (i) 4 Å MS, CH_2Cl_2, −40 °C, 24 h; using catalyst **2h** (10 mol %): 86%, *endo*:*exo* 81:19, 30% ee, using catalyst **2i** (10 mol %): 78%, *endo*:*exo* 81:19, 19% ee.

towards the *endo*-product was observed and full conversion to the desired enantiomerically enriched isoxazolidine (*R*,*R*)-**17** was achieved after 24 h at −35 °C.

Although the obtained enantioselectivities ranged from low to moderate (ee 8–32%), these results provided a sufficient proof of principle for the ability of acids **2a**–**g** to induce enantioselectivity in an acid-catalysed reaction. As expected, a control experiment without any catalyst showed no background reaction (Scheme 5, entry 1).

Due to the significant structural differences and different physical–chemical properties of acids **2a**–**g** and **2h** and **2i**, an independent reaction condition screen was performed for the latter acids. As a result, slightly modified reaction conditions were established for acids **2h** and **2i** (CH_2Cl_2, −40 °C, Scheme 6). Similar to the previous results, acids **2h** and **2i** efficiently catalysed the 1,3-dipolar cycloaddition and gave up to 30% ee of isoxazolidine (*S*,*S*)-**17** (Scheme 6). It is noteworthy that the opposite (*S*,*S*)-enantiomer of the major *endo*-diastereomer **17** was formed in the reactions catalysed by acids **2h**, **2i** when compared to **2a**–**g**.

3. Conclusion

In conclusion, we have successfully designed and executed cross-coupling based syntheses of 2 new classes of stronger chiral Brønsted acids. The catalytic activity and synthetic utility of the novel chiral sulfonic acids have been demonstrated in a highly diastereoselective and enantioselective 1,3-dipolar nitrone/enol ether cycloaddition reaction. Further exploration of the synthetic utility of these and related sulfonic acids is ongoing in our laboratory and the results will be disclosed in due course.

4. Experimental

For all reactions conducted under anhydrous conditions the glassware was dried in an oven at ~100 °C and the reactions were carried out under a nitrogen atmosphere, unless otherwise stated. Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator. Reagents used were obtained from commercial suppliers or purified according to standard procedures. Petrol ether (PE) refers to distilled light petroleum of fraction (40–65 °C). Flash column chromatography was performed with commercial solvents using Merck Kieselgel 60 silica gel (200–400 mesh). Thin layer chromatography (TLC) was performed on aluminium or glass plates pre-coated with Merck Kieselgel 60 F254 and visualised by ultra-violet radiation or by staining with either aqueous basic potassium permanganate or vanillin. Enantiomeric excesses were determined using high performance liquid chromatography (HPLC) performed on a Hewlett–Packard Series 1050 series system (column conditions are given with the compound). Melting points were recorded on a Gallenkamp melting point apparatus with the sample contained in a thin glass tube at ambient pressure and are uncorrected.

Infrared spectra (IR) were recorded on a Perkin Elmer Spectrum RX1 FTIR. Only selected absorbances (ν_{max} in cm^{-1}) are reported. ^1H, ^{13}C, DEPT, COSY and HMQC NMR spectra were recorded on Bruker 500 MHz, Bruker 400 MHz and Varian 300 MHz spectrometers. Chemical shifts (δ_H) are quoted in parts per million (ppm ± 0.01 ppm) downfield of tetramethylsilane, relative to the residual protio solvent (δ_H ($CHCl_3$) = 7.26 ppm) against an internal deuterium lock. Coupling constants (*J*) are given in Hertz (Hz ± 0.1 Hz). The ^1H NMR spectra are reported as follows: δ/ppm (multiplicity, number of protons, coupling constants *J*/Hz, assignment). DEPT and two-dimensional NMR spectroscopy (COSY and HMQC) were used where appropriate to assist the assignment of the signals in the ^1H NMR and ^{13}C NMR spectra. Low resolution mass spectrometry (electron impact/chemical ionisation) was recorded on a Micromass Trio 2000 quadrupole mass spectrometer and (electrospray) on a Micromass Platform II spectrometer. High resolution mass spectra (accurate mass) were recorded on a Thermo Finnigan Mat95XP mass spectrometer. Optical rotations were recorded using an Optical Activity AA-1000 polarimeter; specific rotations ($[\alpha]_D$) are reported in 10^{-1} deg cm^2 g^{-1}; concentrations (*c*) are quoted in g (100 mL)$^{-1}$; D refers to the D-line of sodium (589 nm); temperatures (*T*) are given in degrees Celsius (°C). Compounds **5a**–**d**, **6a**,**b**, **10** and **16** are commercially available, compounds **8a**,[19] **8b**[20] and **15**[22] were prepared according to literature procedures.

4.1. General procedure A for the preparation of C-3 symmetrical *N*-aryloxazolidinones 4a–d

1,3,5-Tribromobenzene **6a** (1 equiv), potassium carbonate (4 equiv), copper(I) iodide (1 equiv) and an oxazolidinone **5** (4 equiv) were placed in a dry flask, and 2 sequences vacuum/nitrogen were applied. Under nitrogen, dry toluene was added (2 mL per mmol), and the suspension was stirred vigorously while *N*,*N*′-dimethylethylenediamine was added in one portion (1 equiv). The resulting dark suspension was refluxed for 18 h (turned blue after few minutes of heating). It was then cooled to room temperature and under nitrogen. When the conversion was not complete, another portion of copper(I) iodide (0.5 equiv), oxazolidinone **5** (1 equiv) as well as *N*,*N*′-dimethylethylenediamine (0.5 equiv) was added, and the suspension refluxed to completion. The mixture was allowed to cool to room temperature and purified by chromatography on silica gel (the large amount of solid can be filtered on Celite prior to purification, washing with ethyl acetate thoroughly).

4.1.1. (4*S*,4′*S*,4″*S*)-3,3′,3″-Benzene-1,3,5-triyltris(4-propyl-1,3-oxazolidin-2-one) 4a

Prepared according to general procedure A, on a 5.22 mmol scale of 1,3,5-tribromobenzene **6a**. Refluxed for 30 h (complete conversion). Purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate (1:1) and the recovered solid was recrystallised from CH_2Cl_2/PE 2:3 to give **4a** (1.12 g, 46%) as a colourless crystalline solid. Mp 83–86 °C; IR 1746 (C=O), 1603 (C=C), 1471 (C=C), 1399 (CH_3); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 0.96 (t, 9H, *J* 7.5 Hz, 3 × CH_3CH$_2$CH$_2$), 1.27–1.47 (m, 6H, 3 × CH$_3$CH_2CH$_2$), 1.58–1.72 (m, 3H, 3 × CH$_3$CH$_2$CH_AH$_B$), 1.76–1.87 (m, 3H, 3 × CH$_3$CH$_2$CH$_A$$H_B$), 4.17 (dd, 3H, *J* 8.0 Hz, 4.0 Hz, 3 × NCHCH_AH$_B$O), 4.41–4.49 (m, 3H, 3 × NCHCH$_A$H$_B$O), 4.49–4.56 (m, 3H, 3 × NCHCH$_A$$H_B$O), 7.60 (s, 3H, *H*-Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 13.8 (*C*H$_3$CH$_2$CH$_2$), 17.4 (CH$_3$*C*H$_2$CH$_2$), 33.8 (CH$_3$CH$_2$*C*H$_2$), 55.9 (N*C*HCH$_2$O), 66.9 (NCH*C*H$_2$O), 108.2 (*C*H-Ar), 138.4 (C_{quat}-Ar), 155.7 (*C*=O); *m*/*z* (ES+) 482 ([M+Na]$^+$, 45%), 941 ([2M+Na]$^+$, 100%), HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{24}H_{33}N_3O_6Na^+$) requires *m*/*z* 482.2262, found *m*/*z* 482.2255; $[\alpha]_D^{25}$ = +142.0 (*c* 1.0, $CHCl_3$).

4.1.2. (4*S*,4′*S*,4″*S*)-3,3′,3″-Benzene-1,3,5-triyltris(4-isopropyl-1,3-oxazolidin-2-one) 4b

Prepared according to general procedure A on a 3 mmol scale of 1,3,5-tribromobenzene **6a**. Refluxed for 18 h + 4 h. Purified on silica gel eluting with PE/EtOAc 1:1 → 2:3 to give **4b** (0.860 g, 62%) as a colourless crystalline solid. Mp 158–161 °C; IR 1745 (C=O), 1603 (C=C), 1473 (C=C), 1402/1393 (CH_3); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 0.88 (d, 9H, *J* 7.0 Hz, 3 × CH_3CHCH$_3$), 0.95 (d, 9H, *J* 7.0 Hz, 3 × CH$_3$CHCH_3), 2.22 (td, 3H, *J* 7.0 Hz, 3.5 Hz, 3 × CH$_3$CHCH$_3$), 4.27 (dd, 3H, *J* 8.0 Hz, 3.5 Hz, 3 × NCHCH_AH$_B$), 4.39–4.49 (m, 6H, 3 × NCHCH$_A$$H_B$), 7.62 (s, 3H, *H*-Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 14.5 (*C*H$_3$CHCH$_3$), 17.8 (CH$_3$CHCH$_3$), 27.7 (CH$_3$*C*HCH$_3$), 60.2 (NCHCH$_2$), 62.6 (NCH*C*H$_2$), 109.7 (*C*H-Ar), 138.4 (C_{quat}-Ar), 155.7 (*C*=O); *m*/*z* (ES+) 482 ([M+Na]$^+$, 100%), HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{24}H_{33}N_3O_6Na^+$) requires *m*/*z* 482.2262, found *m*/*z* 482.2262; $[\alpha]_D^{25}$ = +101.4 (*c* 1.0, $CHCl_3$).

4.1.3. (4*S*,4′*S*,4″*S*)-3,3′,3″-Benzene-1,3,5-triyltris(4-isobutyl-1,3-oxazolidin-2-one) 4c

Prepared according to general procedure A, on a 1.75 mmol scale of 1,3,5-tribromobenzene **6a**. Refluxed for 24 h (complete conversion). Purified by chromatography on silica gel eluting with PE/EtOAc 1:1. The recovered solid was further purified by recrystallisation from PE/EtOAc 1:1 to give **4c** (0.630 g, 72%) as a colourless crystalline solid. Mp 170–174 °C; IR 1754 (C=O), 1603 (C=C), 1471 (C=C), 1398 (CH_3); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 0.96 (d, 9H, *J* 6.5 Hz, 3 × CH_3CHCH$_3$), 1.02 (d, 9H, *J* 6.5 Hz, 3 × CH$_3$CHCH_3), 1.50–1.60 (m, 3H, 3 × CHCH_AH$_B$CH), 1.62–1.74 (m, 3H, 3 × CH$_3$CHCH$_3$), 1.79 (ddd, 3H, *J* 13.0 Hz, 9.0 Hz, 1.5 Hz, 3 × CHCH$_A$$H_B$CH), 4.17 (dd, 3H, *J* 8.0 Hz, 4.0 Hz, 3 × NCHCH_AH$_B$O), 4.47 (ddd, 3H, *J* 10.5 Hz, 7.5 Hz, 3.0 Hz, 3 × NCHCH$_A$H$_B$O), 4.53 (t, 3H, *J* 8.0 Hz, 3 × NCHCH$_A$$H_B$O), 7.63 (s, 3H, *H*-Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 21.7 (*C*H$_3$CHCH$_3$), 23.6 (CH$_3$CHCH$_3$), 24.8 (CH$_3$*C*HCH$_3$), 40.7 (CH*C*H$_2$CH), 54.9 (N*C*HCH$_2$O), 67.3 (NCH*C*H$_2$O), 107.3 (*C*H-Ar), 138.5 (C_{quat}-Ar), 155.2 (*C*=O); *m*/*z* (ES+) 519 ([M+NH$_4$]$^+$, 95%), 560 ([M+CH$_3$CN+NH$_4$]$^+$, 100%), HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{27}H_{39}N_3O_6Na^+$) requires *m*/*z* 524.2731, found *m*/*z* 524.2735; $[\alpha]_D^{25}$ = +171.9 (*c* 1.0, $CHCl_3$).

4.1.4. (4*S*,4′*S*,4″*S*)-3,3′,3″-Benzene-1,3,5-triyltris{4-[(2*S*)-butan-2-yl]-1,3-oxazolidin-2-one} 4d

Prepared according to general procedure A, on a 1.4 mmol scale of 1,3,5-tribromobenzene **6a**. Refluxed for 20 h (complete conversion). Purified by chromatography on silica gel eluting with PE/EtOAc 3:2 → 2:3. The recovered solid was further purified by recrystallisation from PE/EtOAc 2:1 to give **4d** (0.420 g, 60%) as a colourless crystalline solid. Mp 139–143 °C; IR 1748 (C=O), 1603 (C=C), 1472 (C=C), 1400 (CH_3); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 0.87 (d, 9H, *J* 7.0 Hz, 3 × CH_3CH), 0.97 (t, 9H, *J* 7.5 Hz, 3 × CH_3CH$_2$), 1.16–1.29 (m, 3H, 3 × CH$_3$CH_AH$_B$), 1.29–1.40 (m, 3H, 3 × CH$_3$CH$_A$$H_B$), 1.91–2.03 (m, 3H, 3 × CH$_3$CH), 4.25 (dd, 3H, *J* 9.0 Hz, 4.0 Hz, 3 × NCHCH_AH$_B$), 4.41 (t, 3H, *J* 9.0 Hz, 3 × NCHCH$_A$$H_B$), 4.57 (dt, 3H, *J* 9.0 Hz, 4.0 Hz, 3 × NCHCH$_2$), 7.63 (s, 3H, 3 × *H*-Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 11.8 (*C*H$_3$CH), 11.9 (*C*H$_3$CH$_2$), 25.3 (CH$_3$*C*H$_2$), 34.3 (CH$_3$*C*H), 59.0 (NCH), 62.5 (NCHCH$_2$), 109.4 (*C*H-Ar), 138.3 (C_{quat}-Ar), 155.7 (*C*=O); *m*/*z* (ES+) 519 ([M+NH$_4$]$^+$, 95%) 560 ([M+CH$_3$CN+NH$_4$]$^+$, 100%), HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{27}H_{39}N_3O_6Na^+$) requires *m*/*z* 524.2731 found *m*/*z* 524.2737; $[\alpha]_D^{25}$ = +121.1 (*c* 1.0, $CHCl_3$).

4.2. General procedure B for the preparation of C-2 symmetrical *N*-aryloxazolidinones 4e–g

1,3-Dibromo-5-*tert*-butylbenzene **6b** (1 equiv), potassium carbonate (3 equiv), copper(I) iodide (1 equiv) and an oxazolidinone

5 (3 equiv) were placed in a dry flask, and 2 sequences vacuum/nitrogen were applied. Under nitrogen, dry toluene was added (2 mL per mmol), and the suspension was stirred vigorously while *N*,*N*′-dimethylethylenediamine was added in one portion (1 equiv). The resulting dark suspension was refluxed for 24 h (turned blue after few minutes heating). The mixture was then allowed to cool to room temperature under nitrogen and purified by chromatography on silica gel (the large amount of solid can be filtered on Celite prior to purification, washing with ethyl acetate thoroughly).

4.2.1. (4*S*,4′*S*)-3,3′-(5-*tert*-Butyl-1,3-phenylene)bis(4-isopropyl-1,3-oxazolidin-2-one) 4e

Prepared according to general procedure B, on a 2.00 mmol scale of 1,3-dibromo-5-*tert*-butylbenzene **6b**. Refluxed for 24 h. Purified by chromatography on silica gel eluting with PE/Et_2O 1:2 → Et_2O to afford **4e** (0.528 g, 68%) as a colourless solid. Mp 61–63 °C; IR 1746 (C=O), 1601 (C=C), 1457 (C=C), 1393 (CH_3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.87 (d, 6H, *J* 7.0 Hz, 2 × CH_3CHCH$_3$), 0.92 (d, 6H, *J* 7.0 Hz, 2 × CH$_3$CHCH_3), 1.33 (s, 9H, (CH_3)$_3$C), 2.14 (sept. d, 2H, *J* 7.0 Hz, 3.5 Hz, 2 × CH$_3$C*H*CH$_3$), 4.21–4.29 (m, 2H, 2 × NC*H*CH$_2$), 4.38–4.46 (m, 4H, 2 × NCHCH_2), 7.35 (d, 2H, *J* 2.0 Hz, *H*-Ar), 7.37–7.41 (m, 1H, *H*-Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 14.4 (*C*H$_3$CHCH$_3$), 17.7 (CH$_3$*C*HCH$_3$), 27.8 (CH$_3$*C*HCH$_3$), 31.2 ((*C*H$_3$)$_3$C), 35.1 ((CH$_3$)$_3$*C*)), 60.7 (N*C*HCH$_2$), 62.5 (NCH*C*H$_2$), 113.1 (*C*H-Ar), 116.4 (*C*H-Ar), 137.2 (C_{quat}-Ar), 153.3 (C=O), 155.9 (C_{quat}-Ar); *m*/*z* (ES+) 411 ([M+Na]$^+$, 40%), 799 ([2M+Na]$^+$), 100%, HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{22}H_{32}N_2O_4Na^+$) requires *m*/*z* 411.2254, found *m*/*z* 411.2252; $[\alpha]_D^{25}$ = +71.7 (*c* 1.0, $CHCl_3$).

4.2.2. (4*S*,4′*S*)-3,3′-(5-*tert*-Butyl-1,3-phenylene)bis(4-isobutyl-1,3-oxazolidin-2-one) 4f

Prepared according to the general procedure, on a 1.63 mmol scale of 1,3-dibromo-5-*tert*-butylbenzene **6b**. Purified by chromatography on silica gel eluting with PE/EtOAc 7:3 → 1:1 to afford **4f** (0.633 g, 93%) as a colourless crystalline solid. Mp 138–141 °C; IR 1754 (C=O), 1603 (C=C), 1471 (C=C), 1398 (CH_3); ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 0.94 (d, 6H, *J* 6.5 Hz, 2 × CH_3CHCH$_3$), 0.98 (d, 6H, *J* 6.5 Hz, 2 × CH$_3$CHCH_3), 1.33 (s, 9H, (CH_3)$_3$C), 1.51 (ddd, 2H, *J* 13.0 Hz, 10.0 Hz, 4.5 Hz, 2 × CHCH_AH$_B$CH), 1.56–1.68 (m, 2H, 2 × CH$_3$C*H*CH$_3$), 1.73 (ddd, 2H, *J* 13.0 Hz, 10.0 Hz, 3.0 Hz, 2 × CHCH$_A$$H_B$CH), 4.13 (dd, 2H, *J* 8.0 Hz, 5.0 Hz, 2 × NCHCH_AH$_B$O), 4.45 (dddd, 2H, *J* 10.0 Hz, 8.0 Hz, 5.0 Hz, 3.0 Hz, 2 × NC*H*CH$_A$H$_B$O), 4.55 (t, 2H, *J* 8.0 Hz, 2 × NCHCH$_A$$H_B$O), 7.25 (d, 2H, *J* 2.0 Hz, *H*-Ar), 7.54 (t, 1H, *J* 2.0 Hz, *H*-Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 21.7 (*C*H$_3$CHCH$_3$), 23.6 (CH$_3$*C*HCH$_3$), 24.8 (CH$_3$*C*HCH$_3$), 31.2 ((*C*H$_3$)$_3$C)), 35.1 ((CH$_3$)$_3$*C*)), 41.1 (CHCH_2CH), 55.0 (N*C*HCH$_2$O), 67.6 (NCH*C*H$_2$O), 111.9 (*C*H-Ar), 114.8 (*C*H-Ar), 137.3 (C_{quat}-Ar), 153.3, 155.5 (C_{quat}-Ar, *C*=O); *m*/*z* (ES+) 439 ([M+Na]$^+$, 40%), 855 ([2M+Na]$^+$, 100%, HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{24}H_{36}N_2O_4Na^+$) requires *m*/*z* 439.2567, found *m*/*z* 439.2566; $[\alpha]_D^{25}$ = +108.9 (*c* 1.0, $CHCl_3$).

4.2.3. (4*S*,4′*S*)-3,3′-(5-*tert*-Butyl-1,3-phenylene)bis{4-[(2*S*)-butan-2-yl]-1,3-oxazolidin-2-one} 4g

Prepared according to general procedure B, on a 1.47 mmol scale of 1,3-dibromo-5-*tert*-butylbenzene **6b**. Purified by chromatography on silica gel eluting with PE/EtOAc 7:3 → 1:1 to give a solid that was crystallised from EtOAc/Et_2O/PE (1:2:4, 7 mL), affording **4g** (0.525 g, 86%) as a colourless crystalline solid. Mp 123–125 °C; IR 1748 (C=O), 1601 (C=C), 1458 (C=C), 1399 (CH_3); ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 0.87 (d, 6H, *J* 6.5 Hz, 2 × CH_3CH), 0.95 (t, 6H, *J* 7.5 Hz, CH_3CH$_2$), 1.17–1.37 (m, 13H, (CH_3)$_3$C, 2 × CH$_3$CH_2), 1.85–1.95 (m, 2H, 2 × CH$_3$C*H*), 4.24 (dd, 2H, *J* 9.0 Hz, 4.5 Hz, 2 × NCHCH_AH$_B$), 4.41 (t, 2H, *J* 9.0 Hz, 2 × NCHCH$_A$$H_B$), 4.51–4.57 (m, 2H, 2 × NC*H*CH$_A$H$_B$), 7.34 (d, 2H, *J* 2.0 Hz, *H*-Ar), 7.44 (t, 1H, *J* 2.0 Hz, *H*-Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 11.7 (*C*H$_3$CH), 11.9 (*C*H$_3$CH$_2$), 25.3 (CH$_3$*C*H$_2$), 31.2 ((*C*H$_3$)$_3$C)), 34.3 (CH$_3$*C*H), 35.1 ((CH$_3$)$_3$*C*), 59.2 (NCHCH$_2$), 62.4 (NCHCH$_2$), 112.6 (*C*H-Ar), 115.9 (*C*H-Ar), 137.1 (C_{quat}-Ar), 153.3 (*C*=O), 155.9 (C_{quat}-Ar); *m*/*z* (ES+) 439 ([M+Na]$^+$, 40%), 855 ([2M+Na]$^+$, 100%, HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{24}H_{36}N_2O_4Na^+$) requires *m*/*z* 439.2567, found *m*/*z* 439.2569; $[\alpha]_D^{25}$ = +76.2 (*c* 1.0, $CHCl_3$).

4.3. General procedure C for the preparation of sulfonic acids 2a–g

In a dry flask under nitrogen, the substituted *N*-aryl oxazolidinone **4** (1 equiv) was dissolved in dry chloroform (30–50 mL per mmol). The solution was stirred vigorously at room temperature while chlorosulfonic acid (10 equiv) was added dropwise. The cloudy solution was then heated at reflux, with a reverse Dean–Stark apparatus (heavy solvent goes back in the flask) for 24–48 h. The resulting brown biphasic mixture was allowed to cool down to room temperature and poured onto ice (50 mL per mmol), washing the flask twice with dichloromethane (5 mL per mmol each time) and three times with DI water (10 mL per mmol each time). The aqueous phase was collected and the organic layer was extracted with DI water (5 × 20 mL per mmol). Aqueous layers were combined and concentrated under reduced pressure to give a brown oily residue which was purified by column chromatography on silica gel and/or crystallisation.

The acids purified by column chromatography were placed into 1 M HCl (1 mL per 0.100 g of acid) and stirred with CH_2Cl_2 (1 mL per 0.100 g of acid). The organic phase was separated and the aqueous phase was extracted with $CHCl_3$/isopropanol 4:1 (2 × 1 mL per 0.100 g of acid). The combined organics were concentrated in vacuo and dried to give free acid **2**.

4.3.1. 2,4,6-Tris[(4*S*)-4-propyl-2-oxo-1,3-oxazolidin-3-yl]benzenesulfonic acid 2a

Prepared according to general procedure C on a 2.17 mmol of **4a**. Refluxed for 36 h. Purified by chromatography on silica gel eluting with CH_2Cl_2/MeOH 9:1 to give 1.15 g of a light brown solid that was crystallised from hot water (30 mL) to afford **2a** (0.540 g, 47%) as colourless crystals. Mp (water) 231–235 °C (dec); IR 3430 (OH), 2962 (C–H), 1745 (C=O), 1200 (SO_3), 1064 (SO_3); ^{1}H NMR (DMSO-d_6, 500 MHz) δ_H 0.86–0.91 (m, 9H, CH$_2$CH_3), 1.16–1.41 (m, 6H, 3 × CH_2CH$_3$), 1.45–1.74 (m, 6H, 3 × CH_2CH$_2$CH$_3$), 4.04 (dd, 2H, *J* 8.0 Hz, 4.5 Hz, NCHCH_AH$_B$), 4.19 (dd, 1H, *J* 8.5 Hz, 4.5 Hz, NCHCH_AH$_B$), 4.47 (t, 2H, *J* 8.0 Hz, NCHCH$_A$$H_B$), 4.56 (t, 1H, *J* 8.5 Hz, NCHCH$_A$$H_B$), 4.65–4.75 (m, 3H, NC*H*), 7.35 (s, 2H, *H*-Ar); ^{13}C NMR (DMSO-d_6, 500 MHz, 373 K) δ_C 13.0 (CH$_2$*C*H$_3$), 13.2 (CH$_2$*C*H$_3$), 16.2 (*C*H$_2$CH$_3$), 16.7 (*C*H$_2$CH$_3$), 32.9 (CH$_3$*C*H$_2$CH$_2$), 34.2 (CH$_3$CH$_2$*C*H$_2$), 54.3 (*C*H), 57.4 (*C*H), 66.3 (NCH*C*H$_2$O), 67.2 (NCH*C*H$_2$O), 123.7 (*C*H-Ar), 135.3 (NC$_{quat}$-Ar), 136.4 (NC$_{quat}$-Ar), 141.0 (HO$_3$S*C*$_{quat}$-Ar), 154.2 (*C*=O), 155.6 (*C*=O); *m*/*z* (ES−) 538 ([M−H]$^-$, 100%), HRMS (ES−) exact mass calculated for [M−H]$^-$ ($C_{24}H_{32}N_3O_9S^-$) requires *m*/*z* 538.1865, found *m*/*z* 538.1854; $[\alpha]_D^{25}$ = +26.2 (*c* 1.0, MeOH).

4.3.2. 2,4,6-Tris[(4*S*)-4-isopropyl-2-oxo-1,3-oxazolidin-3-yl]benzenesulfonic acid 2b

Prepared according to general procedure C on a 1.85 mmol scale of **4b**. Refluxed for 48 h. Purified by recrystallisation from acetonitrile to afford **2b** (0.470 g, 47%) as colourless crystals suitable for single crystal X-ray diffraction studies. Mp (acetonitrile) 130–133 °C (dec); IR 3400 (OH), 2965 (C–H), 1752 (C=O), 1395 (CH_3), 1202 (SO_3), 1056 (SO_3); ^{1}H NMR (DMSO-d_6, 500 MHz) δ_H 0.76 (d, 3H, *J* 6.9 Hz, CH_3CHCH$_3$), 0.80 (d, 6H, *J* 6.9 Hz, 2 × CH_3CHCH$_3$), 0.89 (d,

3H, *J* 6.9 Hz, CH_3CHCH_3), 0.95 (d, 6H, *J* 6.9 Hz, 2 × CH_3CHCH_3), 1.73–1.83 (m, 2H, 2 × CH_3CHCH_3), 1.98 - 2.06 (m, 1H, CH_3CHCH_3), 2.07 (s, 1H, CH_3CN, ratio **2b**:CH_3CN 1:1), 4.18 (dd, *J* 8.4, 3.3 Hz, 2H, 2 × $NCHCH_AH_BO$), 4.26–4.37 (m, 3H, 2 × $NCHCH_AH_BO$, $NCHCH_AH_BO$), 4.39–4.47 (m, 3H $NCHCH_AH_BO$, 2 × $NCHCH_AH_BO$), 4.73 (dt, 1H, *J* 8.5, 3.5 Hz, $NCHCH_AH_BO$), 7.42 (s, 2H, *H*-Ar); ^{13}C NMR (DMSO-d_6, 125 MHz) δ_C 1.2 (CH_3CN), 14.2 (CH_3CHCH_3), 14.7 (CH_3CHCH_3), 17.1 (CH_3CHCH_3), 17.7 (CH_3CHCH_3), 27.3 (CH_3CHCH_3), 28.3 (CH_3CHCH_3), 58.6 ($NCHCH_2$), 62.50, 62.53 ($NCHCH_2$, $NCHCH_2O$), 63.4 ($NCHCH_2O$), 118.1 (CH_3CN), 123.7 (*C*H-Ar), 135.7 (C_{quat}-Ar), 137.0 (C_{quat}-Ar), 140.3 (C_{quat}-Ar), 154.9 (*C*=O), 156.6 (*C*=O); *m*/*z* (ES−) 538 ([M−H]$^-$, 100%), HRMS (ES−) exact mass calculated for [M−H]$^-$ ($C_{24}H_{32}N_3O_9S^-$) requires *m*/*z* 538.1865, found *m*/*z* 538.1871; $[\alpha]_D^{25}$ = +42.1 (*c* 1.0, MeOH).

Single crystal X-ray diffraction data were collected at 150 K[23] with a Nonius Kappa-CCD diffractometer and processed with Denzo-SMN/SCALEPACK[24] as per the SI (CIF). The structure was solved with SuperFlip[25] and refined with CRYSTALS.[26] The structure is highly disordered with one isopropyl-oxo-oxazolidin modelled in two possible orientations. The compound is reported as the sulfonate hydroxonium salt based on the S–O bond distances (which are statistically indistinguishable) and the hydrogen bonding in the solvent/water sphere. Careful examination of the difference Fourier map in the solvent region, although suggestive of further disorder in the solvent space, supports this conclusion. Full crystallographic data (in CIF format) are available as ESI and has been deposited with the Cambridge Crystallographic Data Centre (reference code 1027606).

4.3.3. 2,4,6-Tris[(4*S*)-4-isobutyl-2-oxo-1,3-oxazolidin-3-yl]benzenesulfonic acid 2c

Prepared according to general procedure C on a 1.26 mmol of **4c**. Refluxed for 48 h. Purified by chromatography on silica gel eluting with dichloromethane/methanol 9:1 to give **2c** (0.640 g, 88%) as a light yellow amorphous solid. Acid **2c** exists in DMSO-d_6 as a mixture of rotamers (according to ^1H and ^{13}C NMR at room temperature). This observation was confirmed by variable temperatures (VT) NMR in DMSO-d_6 at 100 °C. Mp 242–245 °C (dec); IR 3468 (OH), 2958 (C–H), 1751 (C=O), 1201 (SO_3), 1087 (SO_3), 758 (ArCH OOP); ^1H NMR (DMSO-d_6, 500 MHz, 298 K) δ_H *Major rotamer* 0.75 (d, 6H, *J* 6.6 Hz, 2 × CH_3CHCH_3), 0.84 (d, 6H, *J* 6.6 Hz, 2 × CH_3CHCH_3), 0.87 (d, 3H, *J* 6.6 Hz, CH_3CHCH_3), 0.94 (d, 3H, *J* 6.6 Hz, CH_3CHCH_3), 1.35–1.60 (m, 8H, 2 × $CHCH_2CH$, 2 × CH_3CHCH_3, $CHCH_2CH$), 1.61–1.69 (m, 1H, CH_3CHCH_3), 4.07 (dd, 2H, *J* 8.0 Hz, 5.0 Hz, 2 × $NCHCH_AH_BO$), 4.21 (dd, 1H, *J* 8.5 Hz, 4.5 Hz, $NCHCH_AH_BO$), 4.43–4.53 (m, 2H, 2 × $NCHCH_AH_B$), 4.58 (t, 1H, *J* 8.0 Hz, $NCHCH_AH_BO$), 4.65 (app. tt, 2H, *J* 9.0 Hz, 4.5 Hz, 2 × NCH), 4.66–4.76 (m, 1H, NCH), 7.31 (s, 2H, *H*-Ar); ^{13}C NMR (DMSO-d_6, 125 MHz, 298 K) δ_C 21.7 (CH_3CHCH_3), 21.9 (CH_3CHCH_3), 23.48 (CH_3CHCH_3), 23.54 (CH_3CHCH_3), 24.0 (CH_3CHCH_3), 24.1 (CH_3CHCH_3), 40.3 ($CHCH_2CH$), 42.0 ($CHCH_2CH$), 53.4 (NCH), 56.7 (NCH), 67.1 ($NCHCH_2O$), 67.2 ($NCHCH_2O$), 124.6 (*C*H-Ar), 135.5 (C_{quat}-Ar), 136.9 (C_{quat}-Ar), 140.6 (C_{quat}-Ar), 154.7 (C=O), 156.3 (C=O); ^1H NMR (DMSO-d_6, 500 MHz, 298 K) *Minor rotamer* (observable) 0.65 ('t', 6H, *J* 6.0 Hz, 2 × CH_3CHCH_3), 0.74 (d, 3H, *J* 6.5 Hz, CH_3CHCH_3), 1.04–1.10 (m, 1H, CH_3CHCH_3), 1.73–1.83 (m, 1H, $CHCH_AH_BCH$), 3.80–3.87 (m, 1H, $NCHCH_AH_BO$), 3.98–4.03 (m, 1H, NCH), 5.00–5.09 (m, 1H, NCH), 7.26 (br d, 1H, *J* 1.9 Hz, *H*-Ar), 7.52 (s, 1H, *J* 2.2 Hz, *H*-Ar); ^{13}C NMR (DMSO-d_6, 125 MHz, 298 K) *Minor rotamers* (observable) 21.95, 22.06, 22.9, 23.2, 23.4 23.9, 24.2 (CH_3CHCH_3), 40.4, 41.9 ($CHCH_2CH$), 54.0, 55.6, 58.3, 67.3, 68.8, 68.9 ($NCHCH_2O$), 123.0, 125.1, 136.0, 136.4, 137.4, 142.0, 154.7, 156.1, 156.2 (*C*H-Ar, C_{quat}-Ar, *C*=O).

4.3.3.1. VT NMR. ^1H NMR (DMSO-d_6, 500 MHz, 373 K) δ_H 0.79 (d, 6H, *J* 6.0 Hz, 2 × CH_3CHCH_3), 0.85 (d, 6H, *J* 5.5 Hz, 2 × CH_3CHCH_3), 0.91 (d, 3H, *J* 6.5 Hz, CH_3CHCH_3), 0.96 (d, 3H, CH_3CHCH_3, *J* 6.5 Hz), 1.40–1.62 (m, 8H, 2 × $CHCH_2CH$, 2 × CH_3CHCH_3, $CHCH_2CH$), 1.63–1.74 (m, 1H, CH_3CHCH_3), 4.02 (m, 2H, 2 × $NCHCH_AH_BO$), 4.19 (dd, 1H, *J* 8.5 Hz, 4.5 Hz, $NCHCH_AH_BO$), 4.51 (t, 2H, *J* 8.0 Hz, 2 × $NCHCH_AH_BO$), 4.60 (t, 1H, *J* 8.0 Hz, $NCHCH_AH_BO$), 4.66 (ddd, 1H, *J* 13.0 Hz, 8.5 Hz, 4.5 Hz, NCH), 4.76 (br, 2H, 2 × NCH), 7.31 (s, 2H, *H*-Ar); ^{13}C NMR (DMSO-d_6, 125 MHz, 373 K) δ_C 22.3 (CH_3CHCH_3), 22.5 (CH_3CHCH_3), 23.5 (br, CH_3CHCH_3), 23.7 (CH_3CHCH_3), 24.5 (CH_3CHCH_3), 24.7 (CH_3CHCH_3), 40.5 ($CHCH_2CH$), 42.6 (br, $CHCH_2CH$), 54.4 (NCH), 67.8 (CH_2O), 68.9 (br, CH_2O), 125.2 (br, *C*H-Ar), 136.4 (C_{quat}-Ar), 155.1 (C=O), 156.7 (C=O) (the other carbons were not detected at 373 K); *m*/*z* (ES−) 580 ([M−H]$^-$, 100%), HRMS (ES−) exact mass calculated for [M−H]$^-$ ($C_{27}H_{38}N_3O_9S^-$) requires *m*/*z* 580.2334, found *m*/*z* 580.2323; $[\alpha]_D^{25}$ = +30.7 (*c* 1.0, MeOH).

4.3.4. (2,4,6-Tris{(4*S*)-4-[(2*S*)-butan-2-yl]-2-oxo-1,3-oxazolidin-3-yl}benzenesulfonic acid 2d

Prepared according to general procedure C on a 0.80 mmol scale of **4d**. Refluxed for 24 h. Purified by chromatography on silica gel eluting with CH_2Cl_2/MeOH 95:5 → 93:7 to give 0.450 g of a pale brown amorphous solid that was crystallised from CH_2Cl_2 to afford **2d** (250 mg, 54%) as light tan crystals. Mp 166–168 °C (dec); IR 3435 (OH), 2965 (C–H), 1749 (C=O), 1200 (SO_3), 1053 (SO_3); ^1H NMR (DMSO-d_6, 500 MHz) δ_H 0.75 (d, 3H, *J* 6.5 Hz, $CHCH_3$), 0.82 (t, 6H, *J* 7.5 Hz, 2 × CH_2CH_3), 0.90 (t, 3H, *J* 7.5 Hz, CH_2CH_3), 0.97 (d, 6H, *J* 6.5 Hz, $CHCH_3$), 1.06–1.26 (m, 5H, 2 × CH_2CH_3, $CH_AH_BCH_3$), 1.27–1.39 (m, 1H, $CH_AH_BCH_3$), 1.47–1.58 (m, 2H, 2 × $CHCH_3$), 1.72–1.81 (m, 1H, $CHCH_3$), 4.18 (dd, 2H, *J* 8.5 Hz, 3.0 Hz, 2 × $NCHCH_AH_BO$), 4.32 ('t', 3H, *J* 8.5 Hz, 2 × $NCHCH_AH_BO$, $NCHCH_AH_BO$), 4.42 (t, 1H, *J* 8.5 Hz, $NCHCH_AH_BO$), 4.52 (dt, 2H, *J* 8.5 Hz, 3.0 Hz, 2 × NCH), 4.82–4.87 (m, 1H, NCH), 7.39 (s, 2H, H-Ar); ^{13}C NMR (DMSO-d_6, 125 MHz) δ_C 11.1 ($CHCH_3$), 11.73 , 11.78 (CH_3CH_2, $CHCH_3$), 24.3 (CH_2CH_3), 24.8 (CH_2CH_3), 33.9 ($CHCH_3$), 35.2 ($CHCH_3$), 57.5 (NCH), 62.0 (NCH), 62.4 ($NCHCH_2O$), 63.6 ($NCHCH_2O$), 123.5 (*C*H-Ar), 135.7 (NC_{quat}-Ar), 136.9 (NC_{quat}-Ar), 140.4 (HO_3SC_{quat}-Ar), 155.0 (*C*=O), 156.7 (*C*=O); *m*/*z* (ES−) 580 ([M−H]$^-$, 100%), HRMS (ES−) exact mass calculated for [M−H]$^-$ ($C_{27}H_{38}N_3O_9S^-$) requires *m*/*z* 580.2334 found *m*/*z* 580.2341; $[\alpha]_D^{25}$ = +38.4 (*c* 1.0, MeOH).

4.3.5. 4-*tert*-Butyl-2,6-bis[(4*S*)-4-isopropyl-2-oxo-1,3-oxazolidin-3-yl]benzenesulfonic acid 2e

Prepared according to general procedure C on a 1.0 mmol scale of **4e**. Refluxed for 48 h. Purified by chromatography on silica gel eluting with CH_2Cl_2/MeOH 9:1 to afford **2e** (0.440 g, 94%) as an off-white foamy solid. Mp 260–262 °C (dec); IR 3437 (OH), 2965 (C–H), 1733 (C=O), 1229 (SO_3), 1079 (SO_3), 1035 (SO_3); ^1H NMR (DMSO-d_6, 500 MHz) δ_H 0.81 (d, 6H, *J* 7.0 Hz, 2 × CH_3CHCH_3), 0.99 (d, 6H, *J* 7.0 Hz, 2 × CH_3CHCH_3), 1.28 (s, 9H, $C(CH_3)_3$), 1.73–1.79 (m, 2H, 2 × CH_3CHCH_3), 4.19 (dd, 2H, *J* 8.5 Hz, 3.0 Hz, 2 × $NCHCH_AH_BO$), 4.31 (t, 2H, *J* 8.5 Hz, 2 × $NCHCH_AH_BO$), 4.41 (dt, 2H, *J* 8.5 Hz, 3.0 Hz, 2 × NCH, 7.10 (s, 2H, *H*-Ar); ^{13}C NMR (DMSO-d_6, 125 MHz) δ_C 14.7 (CH_3CHCH_3), 17.7 (CH_3CHCH_3), 28.4 (CH_3CHCH_3), 30.6 ($C(CH_3)_3$), 34.0 ($C(CH_3)_3$), 62.4 (NCH), 63.4 ($NCHCH_2O$), 129.1 (*C*H-Ar), 134.9 (NC_{quat}-Ar), 142.0 (HO_3SC_{quat}-Ar), 151.4 (C_{quat}-Ar), 156.8 (*C*=O); *m*/*z* (ES−) 467 ([M−H]$^-$, 100%), HRMS (ES−) exact mass calculated for [M−H]$^-$ ($C_{22}H_{31}N_2O_7S^-$) requires *m*/*z* 467.1857, found *m*/*z* 467.1860; $[\alpha]_D^{25}$ = +56.7 (*c* 1.0, MeOH).

4.3.6. 4-*tert*-Butyl-2,6-bis[(4*S*)-4-isobutyl-2-oxo-1,3-oxazolidin-3-yl]benzenesulfonic acid 2f

Prepared according to general procedure C on a 1.44 mmol of **4f**. Refluxed for 24 h. Purified by chromatography on silica gel eluting

with CH_2Cl_2/MeOH 95:5 → 93:7 to give 0.633 g of a light tan foamy solid that was recrystallised from CH_2Cl_2/Et_2O (1:2, 3 mL) to afford **2f** (0.350 g, 49%). Acid **2f** exists in DMSO-d_6 as a mixture of rotamers (according to ^{1}H NMR at room temperature). This observation was confirmed by variable temperatures (VT) NMR in DMSO-d_6 at 100 °C. Mp 223–226 °C (dec); IR 3437 (OH), 2958 (C–H), 1740 (C=O), 1227 (SO_3), 1077 (SO_3), 1029 (SO_3), 755 (ArCH OOP); ^{1}H NMR (DMSO-d_6, 500 MHz, 298 K) *Major rotamer* δ_H 0.74 (d, 6H, *J* 6.3 Hz, C*H*$_3$CHCH$_3$), 0.82 (d, 6H, *J* 6.3 Hz, CH$_3$CHC*H*$_3$), 1.28 (s, 9H, C(C*H*$_3$)$_3$), 1.32–1.52 (m, 6H, 2 × NCHC*H*$_2$C*H*), 4.02 (dd, 2H, *J* 7.9 Hz, 5.0 Hz, 2 × NCHC*H*$_A$H$_B$O), 4.43–4.46 (m, 2H, 2 × NCHCH$_A$*H*$_B$O), 4.60 (ddd, 2H, *J* 13.1 Hz, 8.8 Hz, 4.6 Hz, 2 × NC*H*), 7.12 (s, 2H, *H*-Ar); ^{13}C NMR (DMSO-d_6, 125 MHz, 298 K) δ_C 22.0 (*C*H$_3$CHCH$_3$), 23.3 (*C*H$_3$CHCH$_3$), 24.1 (CH$_3$*C*HCH$_3$), 30.7 ((*C*H$_3$)$_3$C), 34.0 ((CH$_3$)$_3$*C*), 41.9 (CHCH$_2$CH), 56.4 (N*C*H), 68.1 (NCH*C*H$_2$O), 130.0 (*C*H-Ar), 134.6 (*C*$_{quat}$-Ar), 141.9 (*C*$_{quat}$-Ar), 151.2 (*C*$_{quat}$-Ar), 156.3 (*C*=O); ^{1}H NMR (DMSO-d_6, 500 MHz, 298 K) *Minor rotamers* (observable) 0.63 ('t', 6H, *J* 6.0 Hz, 2 × C*H*$_3$CHCH$_3$), 0.67–0.70 (m, 3H, C*H*$_3$CHCH$_3$), 0.98–1.06 (m, 1H, CH$_3$C*H*CH$_3$), 1.26 (s, 9H, C(C*H*$_3$)$_3$), 1.75–1.80 (m, 1H, CHC*H*$_A$H$_B$CH), 3.81 (dd, 1H, *J* 10.1 Hz, 8.2 Hz, CHC*H*$_A$H$_B$O), 3.94 (dd, 1H, *J* 7.7 Hz, 6.1 Hz, CHCH$_A$*H*$_B$O), 4.31–4.37 (m, 1H, NC*H*), 4.90–4.96 (m, 1H, NC*H*), 7.38 (d, 1H, *J* 1.6 Hz, *H*-Ar); ^{13}C NMR (DMSO-d_6, 125 MHz, 298 K) *Minor rotamers* δ_C 21.7, 22.3, 22.8, 22.9 (*C*H$_3$*C*HCH$_3$), 30.7 ((*C*H$_3$)$_3$C), 34.2 ((CH$_3$)$_3$*C*), 40.1, 42.9 (CHCH$_2$CH), 55.4, 57.9, 62.0, 68.7, 68.8 (N*C*HCH$_2$O), 126.7, 129.9, 135.0, 135.5, 142.6, 152.0, 156.3, 156.3 (*C*H-Ar, *C*$_{quat}$-Ar, *C*=O).

4.3.6.1. VT NMR. ^{1}H NMR (DMSO-d_6, 500 MHz, 373 K) δ_H 0.74–0.80 (br m, 6H, C*H*$_3$CHCH$_3$), 0.80–0.86 (br m, 6H, CH$_3$CHC*H*$_3$), 1.31 (s, 9H, ((C*H*$_3$)$_3$C)), 1.36–1.60 (br m, 6H, 2 × NCHC*H*$_2$C*H*), 3.95–4.02 (br m, 2H, 2 × NCHC*H*$_A$H$_B$O), 4.49 (t, 2H, *J* 8.0 Hz, 2 × NCHCH$_A$*H*$_B$O), 4.60–4.90 (br m, 2H, 2 × NC*H*), 7.14 (br s, 2H, *H*-Ar); *m*/*z* (ES−) 495 ([M−H]$^-$, 100%), HRMS (ES−) exact mass calculated for [M−H]$^-$ ($C_{24}H_{35}N_2O_7S^-$) requires *m*/*z* 495.2170, found *m*/*z* 495.2173; $[\alpha]_D^{25}$ = +44.4 (*c* 1.0, MeOH).

4.3.7. 2,6-Bis{(4*S*)-4-[(2*S*)-butan-2-yl]-2-oxo-1,3-oxazolidin-3-yl}-4-*tert*-butylbenzenesulfonic acid 2g

Prepared according to general procedure C on a 1.22 mmol scale of **4g**. Refluxed for 24 h. Purified by chromatography on silica gel eluting with CH_2Cl_2/MeOH 95:5 → 93:7 to give **2g** (0.556 g, 92%) as a colourless amorphous solid. Mp 233–236 °C (dec); IR 3436 (OH), 2965 (C–H), 1739 (C=O), 1227 (SO_3), 1078 (SO_3), 1033 (SO_3); ^{1}H NMR (DMSO-d_6, 500 MHz) δ_H 0.82 (t, 6H, *J* 7.5 Hz, 2 × CH$_2$C*H*$_3$), 0.99 (d, 6H, 2 × CHC*H*$_3$, *J* 7.0 Hz), 1.07–1.21 (m, 4H, 2 × C*H*$_2$CH$_3$), 1.28 (s, 9H, C(C*H*$_3$)$_3$), 1.42–1.56 (m, 2H, 2 × C*H*CH$_3$), 4.16 (dd, 2H, *J* 8.5 Hz, 3.0 Hz, 2 × NCHC*H*$_A$H$_B$O), 4.31 (t, 2H, *J* 8.5 Hz, 2 × NCHCH$_A$*H*$_B$O), 4.51 (dt, 2H, *J* 8.5 Hz, 3.0 Hz, 2 × NC*H*CH$_A$H$_B$O), 7.09 (s, 2H, *H*-Ar); ^{13}C NMR (DMSO-d_6, 125 MHz) δ_C 11.7 (CH$_2$CH$_3$, CH*C*H$_3$), 24.8 (*C*H$_2$CH$_3$), 30.5 (C(*C*H$_3$)$_3$), 34.0 (*C*(CH$_3$)$_3$), 35.0 (*C*HCH$_3$), 61.7 (NCHCH$_2$O), 63.4 (NCHCH$_2$O), 129.0 (*C*H-Ar), 134.8 (*C*$_{quat}$-Ar), 142.0 (HO$_3$S*C*$_{quat}$-Ar), 151.3 (C$_{quat}$-Ar), 156.8 (C=O); *m*/*z* (ES−) 495 ([M−H]$^-$, 100%), HRMS (ES−) exact mass calculated for [M−H]$^-$ ($C_{24}H_{35}N_2O_7S^-$) requires *m*/*z* 495.2170, found *m*/*z* 495.2176; $[\alpha]_D^{25}$ = +74.2 (*c* 1.0, MeOH).

4.4. [2-(Ethoxysulfonyl)phenyl]boronic acid 11

To a solution of ethyl benzenesulfonate **10** (15.60 mmol, 2.900 g) in THF (39 mL) was added dropwise *n*-BuLi (1.1 equiv, 17.10 mmol, 6.90 mL of 2.5 M solution in hexanes) at −78 °C. The resulting yellow solution was stirred for 5 h before being quenched with B(OMe)$_3$ (1.5 equiv, 23 mmol, 3.4 g, 4.0 mL) at −78 °C. The resulting mixture was warmed to rt over 1 h and 1 M HCl (40 mL) was added. The resulting mixture was stirred at rt for 12 h. The organic phase was separated and the water phase was extracted with Et_2O (3 × 30 mL). Dried combined organics (Na_2SO_4) were concentrated in vacuo and the residue was recrystallised (PE/Et_2O 5:1) to afford **11** (3.310 g, 92%) as a mixture of the acid with the dehydrated form, which was used in the next step. Further recrystallisation afforded pure **11**. Mp 62–65 °C (PE–Et_2O); IR 3456 (OH), 2988 (C–H), 1338, 1180 (SO_3Et); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.33 (t, 3H, *J* 7.2 Hz, OCH$_2$C*H*$_3$), 4.15 (q, 2H, *J* 7.2 Hz, OC*H*$_2$CH$_3$), 4.88 (br s, 2H, B(O*H*)$_2$), 7.61 (dt, 1H, *J* 7.7 Hz, 1.5 Hz, *H*-Ar), 7.69 (dt, 1H, *J* 7.5 Hz, 1.2 Hz, *H*-Ar), 8.04–8.08 (m, 2H, *H*-Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 14.6 (OCH$_2$*C*H$_3$), 67.7 (O*C*H$_2$CH$_3$), 128.8 (*C*H-Ar), 130.3 (*C*H-Ar), 133.3 (*C*H-Ar), 136.8 (*C*H-Ar), 138.9 (*C*$_{quat}$-Ar); HRMS (FI+) exact mass calculated for [M-H$_2$O]$^+$ ($C_8H_9BO_4S^+$) requires *m*/*z* 212.0309, found *m*/*z* 211.9832.

4.5. Ethyl 2-[(3*R*,6*S*)-6-isopropyl-3-methylcyclohex-1-en-1-yl]benzenesulfonate 12

A mixture of boronic acid **11** (10.50 mmol, 2.414 g), Cs_2CO_3 (10.50 mmol, 3.414 g) and triflate **8a** (8.70 mmol, 2.500 g of triflate) in dimethoxyethane (30 mL) and water (5 mL) was degassed and filled with nitrogen. Next, (Ph$_3$P)$_4$Pd (0.05 equiv, 0.44 mmol, 0.505 g) was added and the mixture was stirred at 70 °C. After all starting material had been consumed (TLC monitoring, 1 h) the mixture was cooled to rt and concentrated in vacuo. Water (35 mL) was added and the mixture was extracted with Et_2O (3 × 10 mL). Dried combined organics (Na_2SO_4) were concentrated in vacuo and the residue was purified by column chromatography (PE → PE/Et_2O 98:2 → PE/Et_2O 95:5) to yield **12** (2.191 g, 78%) as a colourless oil. IR 2958, 2932, 2869 (C–H), 1356, 1182 (SO_3Et); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.70 (d, 3H, *J* 6.8 Hz, C*H*$_3$CHCH$_3$), 0.84 (d, 3H, *J* 6.8 Hz, C*H*$_3$CHCH$_3$), 1.01 (d, 3H, *J* 7.1 Hz, C*H*$_3$CHCH$_2$), 1.27–1.45 (m, 5H, OCH$_2$C*H*$_3$, C*H*$_A$H$_B$CHCHCH$_3$, C*H*$_A$H$_B$CHCH$_3$), 1.48–1.56 (m, 1H, CH$_3$C*H*CH$_3$), 1.77–1.86 (m, 2H, CH$_A$*H*$_B$CHCHCH$_3$, CH$_A$*H*$_B$CHCH$_3$), 2.22–2.29 (m, 1H, CH$_3$C*H*CH$_2$), 2.97 (broad s, 1H, CH$_3$CHC*H*), 3.99–4.12 (m, 2H, OC*H*$_2$CH$_3$), 5.48 (s, 1H, CH–C*H*=C$_{quat}$), 7.30 (dd, 1H, *J* 7.6 Hz, 1.3 Hz, *H*-Ar), 7.37 (td, 1H, *J* 7.7 Hz, 1.3 Hz, *H*-Ar), 7.53 (td, 1H, *J* 7.6 Hz, 1.2 Hz, H-Ar), 7.98 (dd, 1H, *J* 8.1 Hz, 1.3 Hz, *H*-Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 14.7 (OCH$_2$*C*H$_3$), 16.2 (*C*H$_3$CHCH$_3$), 20.9 (CH$_3$CH*C*H$_3$), 21.4 (CHCHCH$_2$), 21.6 (*C*H$_3$CHCH$_2$), 28.4 (CH$_3$CHCH$_3$), 30.5 (*C*H$_2$CHCH$_3$), 31.4 (CH$_2$*C*HCH$_3$), 43.0 (CH$_3$CH*C*H), 66.6 (OCH$_2$CH$_3$), 126.7 (*C*H-Ar), 129.7 (*C*H-Ar), 132.5 (*C*H-Ar), 133.0 (*C*H-Ar), 134.0 (*C*$_{quat}$-Ar), 136.6 (CH–*C*H=C$_{quat}$), 141.1 (*C*$_{quat}$), 143.9 (*C*$_{quat}$); HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{18}H_{26}NaO_3S^+$) requires *m*/*z* 345.1495, found *m*/*z* 345.1497; $[\alpha]_D^{25}$ = +50.7 (*c* 4.02, $CHCl_3$).

4.6. {2-(Ethoxysulfonyl)-3-[(3*R*,6*S*)-6-isopropyl-3-methylcyclohex-1-en-1-yl]phenyl}boronic acid 13

To a solution of benzenesulfonate **12** (3.100 mmol, 1.000 g) in THF (13.2 mL) was added dropwise *n*-BuLi (1.1 equiv, 3.4 mmol, 1.4 mL of 2.5 M solution in hexanes) at −78 °C. The resulting yellow-orange solution was stirred for 6.5 h at −78 °C before being quenched with B(OMe)$_3$ (1.5 equiv, 4.70 mmol, 0.679 g, 0.792 mL) at −78 °C. The resulting mixture was warmed to rt over 1 h, after which 1 M HCl (40 mL) was added and the mixture was stirred at rt for 1 h. The organic phase was separated and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organics were washed (brine, 10 mL), dried (Na_2SO_4) and concentrated in vacuo affording **13** (1.141 g, ~100%) as a colourless oil. The crude product containing a mixture of boronic acid and its dehydrated forms was used in the next step without further purification.

4.7. General procedure D for Suzuki coupling of boronic acid 13 with triflates 8a,b

A mixture of boronic acid **13** (1.5–2 equiv), Cs_2CO_3 (2 equiv) triflate **8** (1 equiv) in dimethoxyethane/water (5:1) was degassed and filled with nitrogen. Next, $(Ph_3P)_4Pd$ (0.05 equiv) was added and the mixture was stirred at 70 °C. After all starting material had been consumed (TLC monitoring, typically 1–2 h) the mixture was cooled to rt and concentrated in vacuo. Water (8.4 mL per mmol of **8**) was added and the mixture was extracted with Et_2O (3 × 8.4 mL per mmol of **8**). Dried combined organics (Na_2SO_4) were concentrated in vacuo and the residue was purified by column chromatography.

4.7.1. Ethyl 2,6-bis[(3*R*,6*S*)-6-isopropyl-3-methylcyclohex-1-en-1-yl]benzenesulfonate 7a

According to general procedure D (for 1.19 mmol, 0.435 g of **13** used 0.030 mmol, 0.034 g of $(Ph_3P)_4Pd$; 0.590 mmol, 0.170 g of triflate **8a**; 1.19 mmol, 0.384 g of Cs_2CO_3; 2.0 ml of dimethoxyethane, 0.4 mL of water at 70 °C for 1 h) **7a** (0.205 g, 76%) was obtained as a colourless oil after column chromatography (PE → PE/Et_2O 98:2 → PE/Et_2O 95:5). IR 2957, 2931, 2869 (C–H), 1355, 1179 (SO_3Et); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 0.77 (d, 6H, *J* 6.8 Hz, 2 × C*H*$_3$CHCH$_3$), 0.86 (d, 6H, *J* 6.8 Hz, 2 × C*H*$_3$CHCH$_3$), 1.04 (d, 6H, *J* 7.0 Hz, 2 × C*H*$_3$CHCH$_2$), 1.30–1.50 (m, 7H, OCH$_2$C*H*$_3$, 2 × C*H*$_A$H$_B$CHCHCH$_3$, 2 × C*H*$_A$H$_B$CHCH$_3$), 1.58–1.65 (m, 2H, 2 × CH$_3$C*H*CH$_3$), 1.79–1.84 (m, 4H, 2 × CH$_A$*H*$_B$CHCHCH$_3$, 2 × CH$_A$*H*$_B$CHCH$_3$), 2.19–2.30 (m, 2H, 2 × CH$_3$C*H*CH$_2$), 2.96 (broad s, 2H, 2 × CH$_3$CHC*H*), 4.05–4.17 (m, 2H, OC*H*$_2$CH$_3$), 5.48 (s, 2H, 2 × CH–C*H*=C$_{quat}$), 7.15 (d, 2H, *J* 7.5 Hz, *H*-Ar), 7.35 (t, 1H, *J* 7.7 Hz, *H*-Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 15.2 (OCH$_2$*C*H$_3$), 16.9 (*C*H$_3$CHCH$_3$), 21.3, 21.4, 21.6 (CH$_3$CH*C*H$_3$, *C*H$_3$CHCH$_2$, *C*H$_2$CHCHCH$_3$), 28.3 (CH$_3$CHCH$_3$), 30.3 (*C*H$_2$CHCH$_3$), 31.2 (CH$_2$*C*HCH$_3$), 43.2 (*C*HCHCH$_3$), 65.6 (O*C*H$_2$CH$_3$), 130.7 (*C*H-Ar), 131.4 (*C*H-Ar), 134.2 (C$_{quat}$), 135.1 (CH*C*H=C$_{quat}$), 142.5 (*C*$_{quat}$), 144.6 (*C*$_{quat}$); HRMS (EI/FI) exact mass calculated for $[M]^+$ ($C_{28}H_{42}O_3S^+$) requires *m*/*z* 458.2855, found *m*/*z* 458.3151; $[\alpha]_D^{25}$ = +78.6 (*c* 0.22, $CHCl_3$).

4.7.2. Ethyl 4′-*tert*-butyl-3-[(3*R*,6*S*)-6-isopropyl-3-methylcyclohex-1-en-1-yl]biphenyl-2-sulfonate 7b

According to general procedure D (for 0.75 mmol, 0.275 g of **13** used 0.025 mmol, 0.029 g of $(Ph_3P)_4Pd$; 0.50 mmol, 0.141 g of triflate **8b**; 0.75 mmol, 0.244 g of Cs_2CO_3; 2.0 ml of dimethoxyethane, 0.4 mL of water at 70 °C for 1 h) **7b** (0.142 g, 83%) was obtained as a colourless oil after column chromatography ((PE → PE/Et_2O 98:2 → PE/Et_2O 95:5). IR 2958, 2933, 2869 (C–H), 1354, 1177 (SO_3Et); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.68 (d, 3H, *J* 6.6 Hz, C*H*$_3$CHCH$_3$), 0.92 (d, 3H, *J* 6.9 Hz, CH$_3$CHC*H*$_3$), 1.03 (t, 3H, *J* 6.9 Hz, OCH$_2$C*H*$_3$), 1.06 (d, 3H, *J* 6.9 Hz, C*H*$_3$CHCH$_2$), 1.33–1.49 (m, 11H, (C*H*$_3$)$_3$C, C*H*$_A$H$_B$CHCHCH$_3$, C*H*$_A$H$_B$CHCH$_3$), 1.60–1.67 (m, 1H, CH$_3$C*H*CH$_3$), 1.85–1.89 (m, 2H, CH$_A$*H*$_B$CHCHCH$_3$, CH$_A$*H*$_B$CHCH$_3$), 2.24–2.35 (m, 1H, CH$_3$C*H*CH$_2$), 3.03–3.12 (m, 1H, CH$_3$CHC*H*), 3.72–3.84 (m, 2H, OC*H*$_2$CH$_3$), 5.63 (s, 1H, CH–C*H*=C$_{quat}$), 7.25 (d, 1H, *J* 7.6 Hz, *H*-Ar), 7.29 (d, 1H, *J* 7.6 Hz, *H*-Ar), 7.37 (broad s, 2H, *H*-Ar), 7.42–7.48 (m, 3H, *H*-Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.5 (OCH$_2$*C*H$_3$), 16.4 (*C*H$_3$CHCH$_3$), 21.0 (CH$_3$CH*C*H$_3$), 21.7, 21.7 (*C*H$_3$CHCH$_2$, *C*H$_2$CHCHCH$_3$), 28.8 (CH$_3$*C*HCH$_3$), 30.3 (*C*H$_2$CHCH$_3$), 31.4, 31.5 ((*C*H$_3$)$_3$C, CH$_2$*C*HCH$_3$), 34.6 ((CH$_3$)$_3$*C*), 43.4 (*C*HCHCH$_3$), 65.7 (OCH$_2$CH$_3$), 124.6 (CH-Ar), 128.6 (C$_{quat}$), 131.4 (CH-Ar), 131.4 (CH-Ar), 131.7 (CH-Ar), 133.7 (C$_{quat}$), 135.3 (CH*C*H=C$_{quat}$), 138.4 (C$_{quat}$), 142.9 (C$_{quat}$), 143.4 (C$_{quat}$), 145.2 (C$_{quat}$), 150.5 (C$_{quat}$); HRMS (ESI+) exact mass calculated for $[M+Na]^+$ ($C_{28}H_{38}NaO_3S^+$) requires *m*/*z* 477.2434, found *m*/*z* 477.2438; $[\alpha]_D^{25}$ = +78.1 (*c* 1.12, $CHCl_3$).

4.8. General procedure E for the synthesis of sodium salts of sulfonic acids 14

A mixture of ester **7** (0.100 g) in EtOH (10 mL) and 1 M NaOH (10 mL) was stirred at reflux. After 14 h the mixture was cooled to rt and concentrated in vacuo. Water (30 mL) was then added and the suspension was stirred at rt for 10 min. The insoluble solid was filtered off, washed (water) and dried to yield the sodium salt of sulfonic acid **14** as a colourless solid.

4.8.1. Sodium 2,6-bis[(3*R*,6*S*)-6-isopropyl-3-methylcyclohex-1-en-1-yl]benzenesulfonate 14a

According to general procedure E (for 1.07 mmol, 0.490 g of the ester **7a** used 66 mL of 1 M solution of NaOH, 66 mL of EtOH) the salt **14a** (0.480 g, 99%) was obtained as a colourless solid. Mp 152–156 °C; IR 2957, 2929, 2868 (C–H), 1366, 1191 (SO_3); ^1H NMR (DMSO-d_6, 500 MHz) δ_H 0.69 (d, 6H, *J* 6.8 Hz, 2 × C*H*$_3$CHCH$_3$), 0.76 (d, 6H, *J* 6.8 Hz, 2 × C*H*$_3$CHCH$_3$), 0.94 (d, 6H, *J* 6.9 Hz, 2 × C*H*$_3$CHCH$_2$), 1.27–1.35 (m, 4H, 2 × C*H*$_A$H$_B$CHCHCH$_3$, 2 × C*H*$_A$H$_B$CHCH$_3$), 1.57–1.71 (m, 6H, 2 × CH$_3$C*H*CH$_3$, 2 × CH$_A$*H*$_B$CHCHCH$_3$, 2 × CH$_A$*H*$_B$CHCH$_3$), 2.06–2.17 (m, 2H, 2 × CH$_3$C*H*CH$_2$), 3.15 (broad s, 2H, 2 × CH$_3$CHC*H*), 5.15 (s, 2H, 2 × CH–C*H*=C$_{quat}$), 6.82 (d, 2H, *J* 7.3 Hz, *H*-Ar), 7.04 (t, 1H, *J* 7.6 Hz, *H*-Ar); ^{13}C NMR (DMSO-d_6, 125 MHz) δ_C 16.9 (*C*H$_3$CHCH$_3$), 21.1 (CH$_3$CHCH*C*H$_2$), 21.3 (CH$_3$CH*C*H$_3$), 21.9 (*C*H$_3$CHCH$_2$), 27.7 (CH$_3$*C*HCH$_3$), 29.9 (*C*H$_2$CHCH$_3$), 30.6 (CH$_2$*C*HCH$_3$), 42.1 (*C*HCHCH$_3$), 125.8 (*C*H-Ar), 129.5 (*C*H-Ar), 130.4 (CH*C*H=C$_{quat}$), 141.6 (*C*$_{quat}$), 144.8 (*C*$_{quat}$), 145.1 (*C*$_{quat}$); HRMS (ESI+) exact mass calculated for $[M-Na^+]^-$ ($C_{26}H_{37}O_3S^-$) requires *m*/*z* 429.2469, found *m*/*z* 429.2477; $[\alpha]_D^{25}$ = +51.3 (*c* 1.18, MeOH).

4.8.2. Sodium 4′-*tert*-butyl-3-[(3*R*,6*S*)-6-isopropyl-3-methylcyclohex-1-en-1-yl]biphenyl-2-sulfonate 14b

According to general procedure E (for 0.22 mmol, 0.102 g of **7b** used 11 mL of 1.0 M NaOH, 11 mL of EtOH) **14b** (0.094 g, 91%) was obtained as a colourless solid. Mp 288–290 °C; IR (film) 2957, 2931, 2868 (C–H), 1364, 1218 (SO_3); ^1H NMR (DMSO-d_6, 500 MHz) δ_H 0.57 (d, 3H, *J* 6.9 Hz, C*H*$_3$CHCH$_3$), 0.79 (d, 3H, *J* 6.9 Hz, CH$_3$CHC*H*$_3$), 0.94 (d, 3H, *J* 6.9 Hz, C*H*$_3$CHCH$_2$), 1.24–1.31 (m, 11H, (C*H*$_3$)$_3$C, C*H*$_A$H$_B$CHCHCH$_3$, C*H*$_A$H$_B$CHCH$_3$), 1.53–1.63 (m, 1H, CH$_3$C*H*CH$_3$), 1.64–1.76 (m, 2H, CH$_A$*H*$_B$CHCHCH$_3$, CH$_A$*H*$_B$CHCH$_3$), 2.12–2.23 (m, 1H, CH$_3$C*H*CH$_2$), 3.42–3.51 (m, 1H, CH$_3$CHC*H*), 5.26 (broad s, 1H, CH–C*H*=C$_{quat}$), 6.91 (d, 1H, *J* 7.6 Hz, *H*-Ar), 6.99 (d, 1H, *J* 7.3 Hz, *H*-Ar), 7.17 (t, 1H, *J* 7.3 Hz, *H*-Ar), 7.25 (d, 2H, *J* 8.5 Hz, *H*-Ar), 7.35 (d, 2H, *J* 8.2 Hz, *H*-Ar); ^{13}C NMR (DMSO-d_6, 125 MHz) δ_C 16.4 (*C*H$_3$CHCH$_3$), 21.0 (CH$_3$CHCH$_3$), 21.4 (CHCHCH$_2$), 22.0 (*C*H$_3$CHCH$_2$), 28.3 (CH$_3$CHCH$_3$), 30.0 (CH$_2$CHCH$_3$), 30.9 (CH$_2$CHCH$_3$), 31.4 (C(CH$_3$)$_3$), 34.0 (*C*(CH$_3$)$_3$), 41.7 (CH$_3$CHCH), 123.3 (*C*H-Ar), 127.1 (*C*H-Ar), 128.7 (CH-Ar), 129.9 (*C*H-Ar), 130.3, 130.4 (*C*H-Ar, CH–*C*H=C$_{quat}$), 141.0 (C$_{quat}$), 142.0 (C$_{quat}$), 142.7 (C$_{quat}$), 144.0 (C$_{quat}$), 146.6 (C$_{quat}$), 147.1 (C$_{quat}$); HRMS (ESI−) exact mass calculated for $[M-Na^+]^-$ ($C_{26}H_{33}O_3S^+$) requires *m*/*z* 425.2156, found *m*/*z* 425.2164; $[\alpha]_D^{25}$ = +55.5 (*c* 0.55, MeOH).

4.9. General procedure F for the synthesis of sulfonic acids 2h,i from their salt 14

A suspension of Na-salt **14** in 0.5 M HCl (10 mL per 0.100 g) was extracted with Et_2O (10 mL). The organic layer was concentrated by a stream of nitrogen to afford acid **2**.

4.9.1. 2,6-Bis[(3*R*,6*S*)-6-isopropyl-3-methylcyclohex-1-en-1-yl]-benzenesulfonic acid 2h

According to general procedure F (for 0.070 mmol, 0.030 g of **14a** used 3 mL of 0.5 M HCl and 3 mL of Et_2O) **2h** (0.025 g, 86%)

was obtained as a white solid. Mp 76–81 °C; IR 2958, 2932, 2870 (C–H), 1367, 1173 (SO_3); ^{1}H NMR (DMSO-d_6, 500 MHz) δ_H 0.70 (d, 6H, J 6.6 Hz, 2 × CH_3CHCH$_3$), 0.77 (d, 6H, J 6.9 Hz, 2 × CH$_3$CHCH_3), 0.94 (d, 6H, J 6.9 Hz, 2 × CH_3CHCH$_2$), 1.23–1.36 (m, 4H, 2 × CH_AH_BCHCHCH$_3$, 2 × CH_AH_BCHCH$_3$), 1.56–1.69 (m, 6H, 2 × CH$_3$CHCH$_3$, 2 × CH$_A$$H_B$CHCHCH$_3$, 2 × CH$_A$$H_B$CHCH$_3$), 2.08–2.18 (m, 2H, 2 × CH$_3$CHCH$_2$), 3.00–3.13 (m, 2H, 2 × CH$_3$CHCH), 5.19 (broad s, 2H, 2 × CH–CH=C$_{quat}$), 6.87 (d, 2H, J 7.6 Hz, H-Ar), 7.11 (t, 1H, J 7.6 Hz, H-Ar); ^{13}C NMR (DMSO-d_6, 125 MHz) δ_C 16.9 (CH_3CHCH$_3$), 21.1 (CH$_3$CHCHCH_2), 21.3 (CH$_3$CHCH_3), 21.8 (CH_3CHCH$_2$), 27.7 (CH$_3$CHCH$_3$), 29.9 (CH$_2$CHCH$_3$), 30.6 (CH$_2$CHCH$_3$), 42.4 (CHCHCH$_3$), 126.6 (CH-Ar), 129.7 (CH-Ar), 131.2 (CHCH=C$_{quat}$), 141.8 (C$_{quat}$), 143.6 (C$_{quat}$), 144.1 (C$_{quat}$); MS (ES−) m/z (relative intensity) 429.64 (M-H$^+$, 100%); $[\alpha]_D^{25}$ = +52.9 (c 0.38, MeOH).

4.9.2. 4-*tert*-Butyl-3-[(3*R*,6*S*)-6-isopropyl-3-methylcyclohex-1-en-1-yl]biphenyl-2-sulfonic acid 2i

According to general procedure F (for 0.20 mmol, 0.094 g of **14b** used 10 mL of 1.0 M HCl and 20 mL of Et$_2$O) **2i** (0.086 g, 97%) was obtained as a white solid. Mp 78–84 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ_H 0.57 (d, 3H, J 6.6 Hz, CH_3CHCH$_3$), 0.79 (d, 3H, J 6.6 Hz, CH$_3$CHCH_3), 0.94 (d, 3H, J 6.9 Hz, CH_3CHCH$_2$), 1.23–1.33 (m, 11H, (CH_3)$_3$C, CH$_A$$H_B$CHCHCH$_3$, CH$_A$$H_B$CHCH$_3$), 1.53–1.61 (m, 1H, CH$_3CHCH_3$), 1.65–1.71 (m, 2H, CH$_A$$H_B$CHCHCH$_3$, CH$_A$$H_B$CHCH$_3$), 2.14–2.22 (m, 1H, CH$_3CHCH_2$), 3.44 (broad s, 1H, CH$_3CHCH$), 5.27 (broad s, 1H, CH–CH=C$_{quat}$), 6.92 (d, 1H, J 7.3 Hz, H-Ar), 7.00 (d, 1H, J 7.3 Hz, H-Ar), 7.19 (t, 1H, J 7.6 Hz, H-Ar), 7.25 (d, 2H, J 8.5 Hz, H-Ar), 7.34 (d, 2H, J 7.9 Hz, H-Ar); ^{13}C NMR (DMSO-d_6, 125 MHz) δ_C 16.4 (CH_3CHCH$_3$), 21.0 (CH$_3$CHCH_3), 21.4 (CHCHCH$_2$), 22.0 (CH_3CHCH$_2$), 28.3 (CH$_3$CHCH$_3$), 30.0 (CH$_2$CHCH$_3$), 31.0 (CH$_2$CHCH$_3$), 31.4 (C(CH$_3$)$_3$), 34.1 (C(CH$_3$)$_3$), 41.7 (CH$_3$CHCH), 123.4 (CH-Ar), 127.3 (CH-Ar), 128.7 (CH-Ar), 130.0, 130.4, 130.6 (CH-Ar, CH-Ar, CH–CH=C$_{quat}$), 141.0 (C$_{quat}$-Ar), 141.9 (C$_{quat}$-Ar), 142.7 (C$_{quat}$-Ar), 143.6 (C$_{quat}$-Ar), 146.5 (C$_{quat}$-Ar), 147.2 (C$_{quat}$-Ar); MS (ES−) m/z (relative intensity) 425.45 (M-H$^+$, 100%); $[\alpha]_D^{25}$ = +57.5 (c 0.16, MeOH).

4.10. General procedure G for the enantioselective synthesis of isoxazolidines (*R*,*R*)-17 using catalyst 2a–g

Ethyl vinyl ether **16** (1.50 mmol, 0.108 g, 0.143 mL) was added to a mixture of nitrone **15** (0.300 mmol, 0.0590 g) and 4 Å MS (powder, 0.020 g) in $CHCl_3$ (6.0 mL). The resulting mixture was cooled to −35 °C and catalyst **2** (0.0300 mmol) was added under nitrogen. After 24 h $NaHCO_3$ (saturated aqueous solution, 6 mL) was added and the separated aqueous layer was extracted with CH_2Cl_2 (6 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo. The crude mixture was purified by column chromatography (PE/Et$_2$O 98:2 → 95:5) yielding a diastereomeric mixture of isoxazolidines **17** as a colourless solid.[27] The enantiomeric excess was determined by HPLC using a chiral stationary phase (Chiralcel IA column, 99:1 hexanes/*i*-PrOH, 1.0 mL/min, 220 nm, minor enantiomer t_r = 6.2 min, major enantiomer t_r = 8.1 min).[28] All spectroscopic NMR characterisation data (^{1}H and ^{13}C NMR) are in good agreement with the published data.[21]

4.11. General procedure H for the enantioselective synthesis of isoxazolidines (*S*,*S*)-17 using catalyst 2h,i

Ethyl vinyl ether **16** (1.50 mmol, 0.108 g, 0.143 mL) was added to a mixture of nitrone **15** (0.300 mmol, 0.0590 g) and 4 Å MS (powder, 0.020 g) in CH_2Cl_2 (6.0 mL). The resulting mixture was cooled to −40 °C, after which catalyst **2** (0.0300 mmol) was added under nitrogen. After 24 h $NaHCO_3$ (saturated aqueous solution, 6 mL) was added and the separated aqueous layer was extracted with CH_2Cl_2 (6 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo. The crude mixture was purified by column chromatography (PE/Et$_2$O 98:2 → 95:5) yielding a diastereomeric mixture of isoxazolidines **17** as a colourless solid.[27] The enantiomeric excess was determined by HPLC using a chiral stationary phase (Chiralcel AI column, 99:1 hexanes/*i*-PrOH, 1.0 mL/min, 220 nm, major enantiomer t_r = 6.2 min, minor enantiomer t_r = 8.1 min).[28] All spectroscopic NMR characterisation data (^{1}H and ^{13}C NMR) are in good agreement with the published data.[21]

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